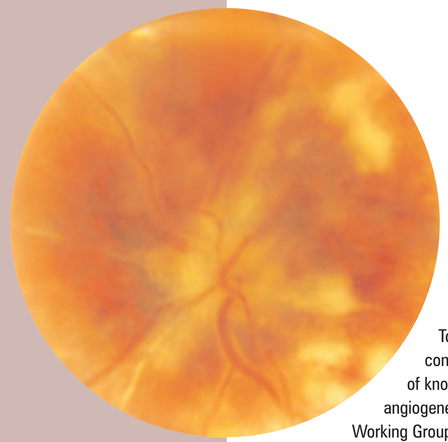
DISCIPLINE-BASED FACULTIES & WORKING GROUPS



Vascular Biology Working Group

Mission

To create an intramural research community committed to the advancement and application of knowledge in the field of vasculogenesis and angiogenesis as applied to cancer treatment. The Working Group accomplishes this goal by promoting research excellence in the field of vascular biology in both the intramural and extramural communities. The Working Group also works to create a research environment that pursues the most creative, cutting-edge, basic and clinical research in vascular biology, both as individual principal investigator-based initiatives and through collaborative interactions. Through these efforts, the Vascular Biology Working Group contributes to the Center for Cancer Research's goal to reduce the burden of cancer.

MEMBERSHIP

All PIs are invited to join. Postdoctoral fellows, staff scientists and fellows, clinical researchers and fellows are welcome to attend seminars and retreats.

AREAS OF INTEREST

This Working Group brings together NCI and other NIH intramural investigators who have interests in topics related to vascular biology. In order to create a program of research excellence and a national effort in discovery and translation of research achievements into novel cancer therapies, the Group's areas of interest include:

- ❖ Developmental vasculogenesis angiogenic growth factors and cytokines
- ❖ Angiogenesis
- ❖ Lymphangiogenesis
- ❖ Vascular pathology
- ❖ Endothelial cells
- ❖ Smooth muscle cell and stem cell biology
- ❖ Animal models
- ❖ Pre-clinical developmental therapeutics
- ❖ Vascular gene profiling
- ❖ Biomarkers
- ❖ Vascular imaging
- ❖ Drug design and development

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Research Interests of Some Vascular Biology Faculty

BILL DAHUT, M.D.

Dr. Dahut's clinical program is focused on developing treatments for metastatic prostate cancer. In that process we have developed an appreciation for the role of angiogenesis in the progression and metastasis of this disease. Thus, we have (or are currently) conducted several trials using agents that inhibit angiogenesis (thalidomide, 2ME, CC5013, and Avastin). With each of those trials, numerous correlative studies are incorporated in order to more fully understand the molecular pharmacology of the agents in patients.

DAVID ROBERTS, PH.D.

Dr. Robert's laboratory is woking on several projects related to identifying or exploiting molecular targets involved in angiogenesis. We have developed stable peptide mimetics that exhibit the antiangiogenic activities of thrombospondin-1 and have shown their activities in several angiogenesis and tumor models. These antagonize FGF2, $\alpha3\beta1$ integrin, $\alpha4\beta1$ integrin, or $\alpha6\beta1$ integrin (reviewed in *Curr. Pharm. Des.* (In press). We were the first to show that $\alpha3\beta1$ and $\alpha4\beta1$ integrin antagonists can inhibit angiogenesis in the chick chorioallantoic membrane (see *Circ. Res.* 94:462-470, 2004). We have also used proteomics and microarrays to identify downstream targets that mediate antiangiogenic signals from thrombospondins and from other known angiogenesis inhibitors (the latter is in collaboration with Dr. Steve Libutti). We identified phosphorylation of cofilin and hsp27 as highly conserved targets of angiogenesis inhibitors (see *Cancer Res.* 63:6405-6412, 2003). Additional targets have been identified that are regulated at the mRNA level (*Genome Res.* 14:1585-1593, 2004).

WILLIAM D. FIGG, PHARM.D.

The laboratory of Dr. Figg has been focused on developing new angiogenesis inhibitors. Through the development of new *in vitro* models to screen agents that have formed a complete drug development program for this target—molecular target identification, computational drug design, synthesis of novel structures, screen agents, optimizing pharmacology, determining structure/activity relationships, *in vitro* testing in preclinical models, preliminary toxicology, and preclinical pharmacokinetics. This group has worked with numerous antiangiogenesis agents over the years, but has spent the last four years on determining the molecular pharmacology of thalidomide and developing analogs with better pharmaceutical properties. To this end, they have patented 61 new analogs and licensed them. Those agents are now moving toward the clinic.

This section also works closely with Dr. Bill Dahut and Dr. Sandy Swain to develop a solid translational program in this field. Many of the ideas developed in the laboratory are tested in the clinical program of these investigators.

WILLIAM STETLER-STEVENSON, M.D., PH.D.

Dr. Stetler-Stevenson's laboratory is focused on the role of the tissue inhibitors of metalloproteinases or TIMPs in regulation of tumor angiogenesis. Our recent work has demonstrated that TIMP-2 inhibits human microvascular endothelial cell proliferation independent of its ability to inhibit metalloproteinase activity. The mechanism of this inhibitory effect involves binding of TIMP-2 to its receptor, the integrin $\alpha3\beta1$. This receptor-ligand interaction results in activation of protein-tyrosine phosphatase activity and inactivation of receptor tyrosine kinase signaling activity. In addition, we have demonstrated that TIMP-2 treatment of human microvascular endothelial cells results in activation of a negative growth regulatory pathway that involves the protein-tyrosine phosphatase Shp-1, cAMP-dependent protein kinase A, and induction of the cyclin-dependent kinase inhibitor $p27^{Kip1}$. Activation of this signaling pathway by TIMP-2 results in G_1 growth arrest as evidenced by flow cytometric cell cycle analysis, reduction in cyclin D protein levels, and pRb hypophosphorylation. In addition, we have also demonstrated that TIMP-2 inhibits human microvascular endothelial cell migration independent of its MMP inhibitory activity by induction of RECK. We demonstrate that TIMP-2–mediated induction of RECK expression in quiescent human microvascular endothelial cells results in colocalization of RECK with MT1-MMP and inhibition of MT1-MMP activity. These findings suggest that TIMP-2 is a potent inhibitor of endothelial cell responses to angiogenic factors such as VEGF-A and FGF-2. Our current goal is to identify small molecule inhibitors of angiogenesis that can mimic the activities of TIMP-2 *in vivo*.

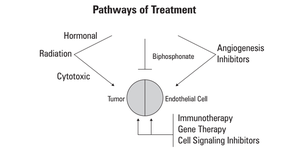
Examples of Collaborations Among the Vascular Biology Faculty Members

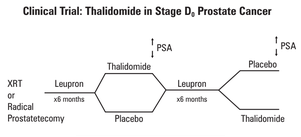
I. CLINICAL DEVELOPMENT OF THALIDOMIDE AND THALIDOMIDE ANALOGS

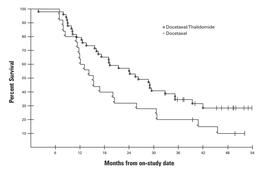
Dahut WL, Gulley JL, Arlen PM, Liu Y, Fedenko KM, Steinberg SM, Wright JJ, Parnes H, Chen CC, Jones E, Parker CE, Linehan WM, **Figg WD**. A Randomized Phase II Trial of Docetaxel plus Thalidomide in Androgen-Independent Prostate Cancer. *J Clin Oncol* 2004;22:2532-9.

Leonard GD, **Dahut WL**, Gulley J, Arlen P, **Figg WD**. Docetaxel and Thalidomide as a Treatment Option in Androgen-Independent Prostate Cancer. *Rev Urol* 2003;5(Suppl 3):S65-70.

Tohnya TM, Ng SS, **Dahut WL**, Wright JJ, Arlen PM, Gulley JL, Parker C, Zeldis J, **Figg WD**. A Phase I Study of Oral CC-5013 (Lenalidomide, Revlimid), a Thalidomide Derivative, in Patients with Refractory Metastatic Cancer. *Clinical Prostate Cancer* 2004;2:241-3.





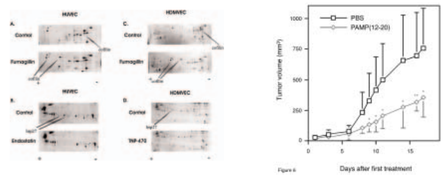


II. DISCOVERY OF CONVERGENT SIGNALING PATHWAYS FOR ANGIOGENESIS INHIBITORS

Keezer SM, Ivie SE, Krutzsch HC, Tandle A, **Libutti S**, and **Roberts DD**. Angiogenesis inhibitors target the endothelial cell cytoskeleton through altered regulation of Hsp27 and cofilin. *Cancer Res* 63:6405-12, 2003.

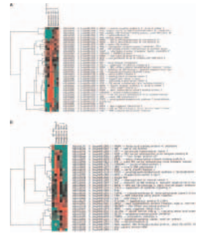
Mazzanti CM, Tandle A, Lorang D, Costouros N, **Roberts DD**, Bevilacqua G, and **Libutti SK**. Early genetic mechanisms underlying the inhibitory effects of endostatin and fumagillin on human endothelial cells. *Genome Res* 14:1585-93, 2004.

Tandle AT, Mazzanti C, Alexander HR, **Roberts DD**, and **Libutti SK**. EMAP-II induced gene expression changes in endothelial cells. (in preparation)



III. DISCOVERY OF A HIGHLY POTENT ANGIOGENIC PEPTIDE

Martinez A, Zudaire E, Portal-Nunez S, Guedez L, **Libutti SK**, **Stetler-Stevenson WG**, **Cuttitta F.** Proadrenomedullin NH2-terminal 20 peptide is a potent angiogenic factor, and its inhibition results in reduction of tumor growth. *Cancer Res* 2004, 64:6489-94.



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